Table I. Bayes' theorem output: relation between pre-test probability, PPV, and 1-NPV for a new melanoma digital dermoscopic analysis

Pre-test probability	PPV	1-NPV
0.01	0.11	0.0008
0.05	0.40	0.004
0.10	0.59	0.01
0.15	0.69	0.01
0.20	0.76	0.02
0.25	0.81	0.02
0.30	0.85	0.03
0.35	0.87	0.04
0.40	0.90	0.05
0.45	0.91	0.06
0.50	0.93	0.07
0.55	0.94	0.08
0.60	0.95	0.10
0.65	0.96	0.12
0.70	0.97	0.15
0.75	0.97	0.18
0.80	0.98	0.23
0.85	0.99	0.30
0.90	0.99	0.40
0.95	0.99	0.59

increase the PPV to 0.59 if the result is positive, or yield an acceptable 1-NPV of 0.004 if the test is negative, and thus provides important information to the clinician attempting to make a difficult decision. Selective use in settings where the decision to biopsy may result in an adverse patient outcome may be a potential use for computerized digital dermoscopy.

When assessing the clinical relevance of diagnostic technology, clinicians must consider a test's PPV and 1-NPV (not just its sensitivity and specificity) and the pre-test probabilities where its use may inform clinical decisions. Whereas Rubegni *et al*'s tool appears to be a powerful diagnostic aid, whether the additional amount of clinical information the tool provides justifies the cost of technology requires us to consider the broad determinants of medical decision-making: physician behavior, disease prevalence, outcome, cost, and values.

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REFERENCES

Giard R, Hermans J: The diagnostic information of tests for the detection of cancer: The usefulness of the likelihood ratio concept. *Eur J Cancer* 32A:2042–2048, 1996

Grimes D, Schultz K: Uses and abuses of screening tests. *Lancet* 359:881–884, 2002

Hagen M: Test characteristic: How good is that test? *Prim Care* 22:213–223, 1995

Rubegni P, Burroni M, Cevenini GM, *et al*: Digital dermoscopy analysis and artificial neural network for the differentiation of clinically atypical pigmented skin lesions: A retrospective study. *J Invest Dermatol* 119:471–474, 2002

Smith JR, Winkler RL, Fryback DG, *et al*: The first positive: Computing positive predictive value at the extremes. *Ann Intern Med* 132:804–809, 2000

Active Human Herpesvirus 6 Infection in a Patient with Drug Rash with Eosinophilia and Systemic Symptoms

To the Editor:

Clinical and biologic manifestations of drug rash with eosinophilia and systemic symptoms (DRESS) are well characterized and mimic viral infection: high fever, facial edema, erythroderma followed by an exfoliative dermatitis, diffuse lymphadenopathy, hypereosinophilia, atypical circulating lymphocytes, abnormal results of liver function tests. Other systemic manifestations may occur (e.g., pneumonitis, pancreatitis, neurologic symptoms). This drug adverse reaction was first described with anticonvulsivants but minocycline is also well known to induce this kind of reaction (Disdier *et al*, 2001).

The role of viral infection in the development of this drug adverse reaction is suspected. We implicated for the first time human herpesvirus 6 (HHV-6) infection in a patient with phenobarbital-induced DRESS complicated by a fulminant hemophagocytic syndrome (Descamps *et al*, 1997). In a small prospective series of seven consecutive patients hospitalized with DRESS we demonstrated serologic evidence of HHV6 active infection (Descamps *et al*, 2001). But evidence of viremia, which is the main criterion for confirmation of active infection, was not demonstrated in these cases (Descamps and Mahe, 2002; Tohyama and Hashimoto, 2002). Recently, we and others reported HHV-6 encephalitis associated with DRESS (Descamps *et al*, 2003). We report here a typical case of DRESS associated with minocycline and bring evidence of viremia by quantification of HHV-6 DNA in serum samples.

A black 25-y-old patient was prescribed minocycline for the treatment of folliculitis on the scalp on the 16 May 2000. Seven weeks later on the 7 July 2000 he developed an erythroderma and

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Abbreviations: DRESS, drug rash with eosinophilia and systemic symptoms; HHV-6, human herpesvirus 6; NR, normal rate.

was hospitalized 5 d later. On examination he had an edema of the face, erythroderma with exfoliative dermatitis, and diffuse lymph node enlargement. Laboratory studies showed on admission a leucocytosis (18.2×10^9 per liter) with many large atypical basophilic lymphocytes (48.2%) with T phenotype CD3 + (96%), CD4 + (87%), CD7 + (70%), CD38 + (56%), CD25 + (22%), CD19 + (1%). Three days later appeared an eosinophilia (1.33×10^9 per liter). Four days later after the admission alanine aminotransferase (223 U per liter, NR < 56) and aspartate aminotransferase (314 U per liter, NR < 56) concentrations increased and then returned to normal values. Histologic examination of skin lesions revealed a dense dermal infiltrate with pleomorphic lymphocytes and atypical cells. HHV-6 infection was studied on serum samples collected on admission (13 July) and at different times after admission (24 July, 2 August). No treatment was given during this period. The presence of anti-HHV-6 IgG and IgM antibodies was determined at the same time in the different serum samples using an indirect immunofluorescent antibody assay (Descamps *et al*, 1997). Anti-HHV-6 IgG serologic tests revealed a rise in the antibody titer from 80 (13 July) to 640 (2 August). Presence of anti-HHV-6 IgM was only demonstrated in the first serum (13 July). A polymerase chain procedure and a real-time HHV-6 quantitative PCR assay were performed on the serum samples (Desachy *et al*, 2001; Collot *et al*, 2002). Detection of HHV-6 DNA was positive on the first two serum samples (13 July and 24 July) and was quantified at 16,909,880 copies per ml and 8400 copies per ml, respectively. It was negative in the third serum. Genotyping of HHV-6 indicated a type B genotype. Serologic investigations for coxsackies A and B, echovirus, HIV, and cytomegalovirus infections were negative. Serologic data supported previous infection with Epstein-Barr virus, toxoplasmosis, and parvovirus B19.

DNA extraction from samples was performed using the QIAamp blood kit (Qiagen, Courtaboeuf, France). For HHV-6 genotyping, a nested PCR was used to amplify a 492 bp fragment on the U31 gene using the outer primers H6/594 (5′-TTA ACG GTC GCG TTC TAA CC-3′) and H6/1809 (5′-ACG CCT CGT TGA ATA CTT CG-3′) and the inner primers H6/772 (5′-AAG AAG GCT ATC ACT TAG ACA CGG-3′) and H6/1263 (5′-TTA GGA TAA GAA GCT CGG CG-3′). This fragment included a HindIII restriction site for HHV-6 type B, absent in type A.

Viral infections are suggested to play a role in some drug-induced eruptions. This is illustrated by the well-known ampicillin-induced eruption in Epstein-Barr virus mononucleosis syndrome. Our report demonstrates HHV-6 viremia of short time duration at the beginning of the DRESS. Tohyama *et al* previously reported isolation of HHV-6 from peripheral blood mononuclear cells in a patient with sulfasalazine-induced DRESS (Pirmohamed *et al*, 2001). Isolation of HHV-6 preceded increase in anti-HHV-6 IgG titers from 1/160 to 1/1280, 8 d later, and no anti-HHV-6 IgM antibody was detected (Tohyama *et al*, 1998).

Detection of HHV-6 DNA in cell-free serum implies replication of HHV-6 in this patient. The quantification of the HHV-6 viral load brings new data to document the association of active HHV-6 infection with DRESS. This may represent either a primary infection or a reactivation of HHV-6. We did not have previous serum of our patient to identify the presence of anti-HHV-6 IgG antibodies before. A primary infection or reinfection cannot be excluded considering the very high level of viral load. But we think that a selective reactivation of HHV-6 with a strong replication is the most probable explanation in this case and others. HHV-6 is the paradigm of opportunistic infectious agent that may reactivate in some conditions. HHV-6 can infect a broad range of human cells: CD4 lymphocytes, macrophages, dendritic cells, epithelial cells, fibroblasts, and bone marrow progenitors. But HHV-6 replication is only demonstrated in activated CD4 lymphocytes. After primary infection, reactivation or reinfection may occur in the case of immune dysregulation or deficiency. Selective replication of HHV-6 was also reported in critically ill nonimmunocompromised patients (Razonable *et al*, 2002). Recently, HHV-6 reactivation was also demonstrated in pityriasis rosea patients (Watanabe *et al*, 2002). It may be proposed that on a genetic background some drugs may induce the production of reactive metabolites that may provoke HHV-6 reactivation and propagation by the way of cytokine production. It was demonstrated that activation of CD4 + lymphocytes with interleukin-2 was essential for propagation of HHV-6 *in vitro*. Recently the frequency of HLA-DR3 and HLA-DQ2 was found to be increased in a group of severe DRESS induced by carbamazepine ($p = 0.01$; odds ratio 3.3, and $p = 0.04$, odds ratio 2.7, respectively) (Pirmohamed *et al*, 2001). Interestingly genotyping of this patient revealed that he was HLA-DR3 (DRB1*0301) and HLA-DQ2 (DQB1*0201) positive.

The role of HHV-6 may be not limited to the initial development of DRESS. HHV-6 replication can lead to systemic viral dissemination to target organs. HHV-6 may also be directly implicated in systemic manifestations in DRESS. Recently, we and others reported HHV-6 encephalitis associated with DRESS suggesting that HHV-6 may be responsible for systemic manifestations such as hepatitis, pancreatitis, and intestinal or meningoencephalitis (Descamps *et al*, 2003).

The link between drug reaction and HHV-6 viral infection could suggest a new therapeutic approach of drug reactions with antiviral agents. For instance HHV-6 U69 gene product is a functional homolog of the human cytomegalovirus UL97 gene and confers sensitivity of HHV-6 infected cells to antiviral drugs such as ganciclovir (Griffiths *et al*, 2000). Valganciclovir, a new oral derivative of ganciclovir that is better tolerated than ganciclovir, could be used in DRESS patients.

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REFERENCES

Collot S, Petit B, Bordessoule D, *et al*: Real-time PCR for HHV-6 DNA quantification in lymph nodes and saliva. *J Clin Microbiol* 40:2445–2451, 2002

Desachy A, Ranger-Rogez S, François B, *et al*: Reactivation of human herpesvirus type 6 in multiple organ failure syndrome. *Clin Infect Dis* 32:197–203, 2001

Descamps V, Mahe E: Drug hypersensitivity syndrome and human herpesvirus 6 reactivation. *Arch Dermatol* 138:269, 2002

Descamps V, Bouscarat F, Laglenne S, *et al*: Human herpesvirus 6 infection associated with anticonvulsant hypersensitivity syndrome and reactive haemophagocytic syndrome. *Br J Dermatol* 137:605–608, 1997

Descamps V, Valance A, Edlinger C, *et al*: Association of human herpesvirus 6 infection with drug reaction with eosinophilia and systemic symptoms. *Arch Dermatol* 137:301–304, 2001

Descamps V, Collot S, Houhou N, Ranger-Rogez S: Human herpesvirus-6 encephalitis associated with hypersensitivity syndrome. *Ann Neurol* 53:280, 2003

Disdier P, Granel B, Serratrice J, Weiller P-J: A teenager with rash and fever. *Lancet* 358:2046, 2001

Griffiths PD, Clark DA, Emery VC: Betaherpesviruses in transplant recipients. *J Antimicrob Chemother* 45 (Suppl T3):29–34, 2000

Pirmohamed M, Lin K, Chadwick D, Park BK: TNF α promoter region gene polymorphisms in carbamazepine-hypersensitive patients. *Neurology* 56:890–896, 2001

Razonable RR, Fanning C, Brown RA, *et al*: Selective reactivation of human herpesvirus 6 variant A occurs in critically ill immunocompetent hosts. *J Infect Dis* 185:110–113, 2002

Tohyama M, Yahata Y, Yasukawa M, *et al*: Severe hypersensitivity syndrome due to sulfasalazine associated with reactivation of human herpesvirus 6. *Arch Dermatol* 134:113–117, 1998

Tohyama M, Hashimoto K: Drug hypersensitivity syndrome and human herpesvirus 6 reactivation. *Arch Dermatol* 138:268–269, 2002

Watanabe T, Kawamura T, Jacob SE, *et al*: Pityriasis rosea is associated with systemic active infection with both human herpesvirus-7 and human herpesvirus-6. *J Invest Dermatol* 119:793–797, 2002